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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,511	10/06/2000	Raymond Andersen	P108281-0000	6795

7590 10/08/2004

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EXAMINER

LUKTON, DAVID

ART UNIT

PAPER NUMBER

1653

DATE MAILED: 10/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/581,511

Applicant(s)

ANDERSEN ET AL.

Examiner

David Lukton

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-78 is/are pending in the application.
- 4a) Of the above claim(s) 74 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 24, 29 and 59 is/are allowed.
- 6) ☒ Claim(s) 22, 26, 28, 30, 34, 61, 62, 64-66, 69, 71-73 and 75-78 is/are rejected.
- 7) ☒ Claim(s) 23, 25, 27, 31-33, 35-58, 60, 63, 67, 68 and 70 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Pursuant to the directives of the amendment filed 12/3/03, claims 22, 24, 26, 28-30, 34, 59, 61, 62, 64-66, 71-73 have been amended, and claims 75-78 added.

Claims 22-78 are now pending. Claim 74 remains withdrawn from consideration at this time. Applicants' arguments filed 7/28/04 have been considered and found persuasive in part. Claims 24, 29 and 59 are characterized as allowable at the present time; claims 23, 25, 27, 31-33, 35-58, 60, 63, 67, 68, 70 are objected to because of their dependence on rejected claims.



The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 73 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown that the compound "SPA-110" can inhibit mitosis of breast cancer cells in vitro. The results of a second experiment (page 27+) can be interpreted to mean that a reduction in the rate of growth of colon carcinoma cells can be achieved *in vivo*.

However, claim 73 recites that a patient afflicted with any tumor can be successfully treated.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. The following references discuss the matter of various attempts by oncologists to treat cancer: Viallet (*Lung Cancer* **15** (3) 367-73, 1996); Kemeny (*Seminars in Oncology* **21** (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* **9** (12) 2815-29, 2000); Giese (*Journal of Cancer Research and Clinical Oncology* **127** (4) 217-25, 2001); Garattini (*European Journal of Cancer* **37** Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* **40** (2-3) 282-308, 2001).

As is evident, attempts to kill cancer cells in tumor-bearing mammals using agents which have exhibited *in vitro* activity leads to "unpredictable" results. In addition, the term "cancer" or "tumor" encompasses a wide variety of proliferative diseases, such as the following: prostate cancer, lung cancer, colon cancer, rectal cancer, bladder cancer, Non-Hodgkin Lymphoma, melanomas of the skin, cancer of the Kidney and Renal Pelvis,

pancreatic cancer, oral cancer, esophagal cancer, ovarian cancer, thyroid cancer, stomach cancer, brain cancer, multiple myeloma, liver and intrahepatic bile duct cancer, acute myeloid leukemia, chronic lymphocytic leukemia, Hodgkin's Lymphoma, testicular cancer, intestinal cancer, chronic myeloid leukemia, acute lymphocytic leukemia, cancer of the vulva, gallbladder cancer, malignant mesothelioma, bone cancer, joint cancer, cancer of the hypopharynx, cancer of the eye, cancer of the nose, cancer of the ureter, cancer of the peritoneum, gastrointestinal carcinoid tumors, bladder cancer, melanoma, breast cancer, non-hodgkin's lymphoma, ovarian cancer, endometrial cancer, pancreatic cancer, kidney cancer (renal cell), prostate cancer, leukemia, non-melanoma cancer of the skin. Also included are sarcomas and carcinomas, such as the following: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma,

oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, lymphoma, multiple myeloma, Waldenström's macroglobulinemia, and heavy chain disease.

There is no evidence of record that there exists any one agent that is effective against all of these cancer types, or most of them. The skilled oncologist would not regard it as realistic that one can extrapolate from a showing of inhibition of growth of one cancer cell type to inhibition of growth of all cancer cell types.

It is suggested that the following phrases be deleted from claim 73:

“suitable for treating tumors”, and

“an anti-tumor effective amount of”.



Claims 22, 34, 61, 62, 64-66, 69, 71, 72, 75-78 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 22, seventh line of text following the structure, there is a hyphen at the end of the line which is unattached to anything.
- Claim 34 is recited to be dependent on claim 22, but it appears that applicants intend for it to be written in independent form.
- In claims 64-66 and 71, substituent variables “Y” and “Z” are defined, but do not appear in the formula.
- In claim 69, the “s” should be capitalized. The following phrase is suggested:

- - a chiral center of the S-configuration - - .

- In claim 61, R₉ is defined as the following: -Y-CO-Z.
Substituent variable "Z", in turn, is defined as OH only. However, a substituent variable is just that, i.e., a "variable" assumes more than one possibility. In claim 61, "Z" can be only one possibility; accordingly, both "Z" and its definition should be deleted from the claim. As such, R₉ should be defined simply as: -Y-COOH.
Similarly, in claim 62, R₉ should be defined simply as: -Y-COOCH₃.
- In each of claims 75-78, R₆ is defined as a hydrogen atom only. As such, variable R₆ is not a variable, but a "constant". Accordingly, both "R₆" and its definition should be deleted from the claim; a hydrogen atom can simply be inserted into the formula.
- In claim 72, a series of variables are each assigned a single substituent. However, a variable permits multiple possibilities. It is suggested that claim 72 be re-written in either dependent form or independent form, but without reference to any substituent variables.



The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

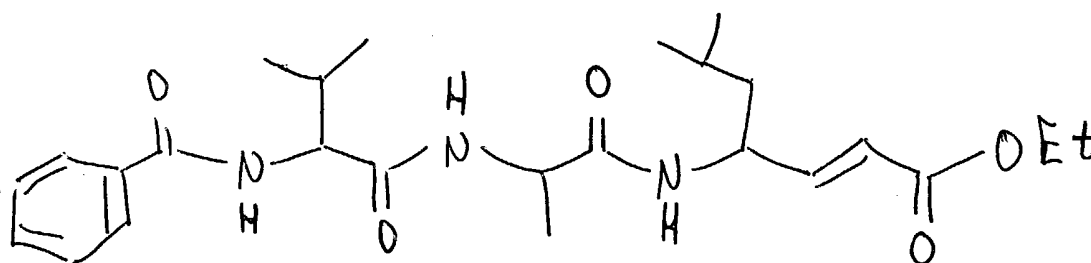
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 22, 26, 28, 30, 61, 75 are rejected under 35 U.S.C. §102(a) as being anticipated by Johnson (WO 97/04004).

Johnson discloses compound 26 (page 74), which has the following structure:



The disclosed compound (compound 26, page 74, Johnson) is encompassed by claim 22 when the substituent variables are as follows:

- R1 = hydrogen;
- R2 = benzoyl;
- R3 = methyl;
- R4 = methyl;
- R5 = hydrogen;
- R6 = hydrogen
- R7 = methyl
- R8 = hydrogen
- Y = propylene substituted with isobutyl
- Z = -O-CH₂-CH₃

Thus, the claims are anticipated.



Claim 61 is rejected under 35 U.S.C. §102(b) as being anticipated by Reetz (*Angew. Chem., Int. Ed. Engl.*, **31**(12), 1626-9, 1992).

Reetz discloses compound 11 (page 1627, col 2). This compound would correspond to the substituent variables of claim 22 as follows, if not for one of the provisos:

R1 = hydrogen
R2 = tBoc
R3 = hydrogen
R4 = hydrogen
R5 = phenyl
R6 = hydrogen
R7 = methyl
R8 = hydrogen
Y = propylene substituted with isobutyl
Z = -O-CH₂-CH₃

As it happens, claim 22 excludes the possibility that R2 (or R1) can be *tert*-butyloxycarbonyl. However, the issue now raised pertains to the term "having". That is, the claim is not drawn to a compound "of" the formula; rather, the claim is drawn to a compound "having" the indicated formula. As such, the claim would permit additional substituents to be added to the N- or C-terminus. This ground of rejection then is not based on R₂ being tBoc; rather, it is based on R1 and R2 both representing hydrogen. Since the claimed peptide "has" the indicated structure, rather than consists of it, the claims would permit an additional substituent, such as tBoc, to be bonded to the N-terminus. The same argument applies in the case of "Z".



Claim 75 is rejected under 35 U.S.C. §102(b) as being anticipated by Reetz (*Angew. Chem., Int. Ed. Engl.*, **31**(12), 1626-9, 1992).

As indicated above, Reetz discloses compound 11 (page 1627, col 2). This compound corresponds to the substituent variables of claim 22 as follows:

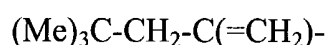
R1 = hydrogen
R2 = tBoc
R3 = hydrogen
R4 = hydrogen
R5 = phenyl
R6 = hydrogen
R7 = methyl
R8 = hydrogen
Y = propylene substituted with isobutyl
Z = -O-CH₂-CH₃

There is an issue concerning variable R₂. Variable R₂ is defined as follows:

“R₁ and R₂ are independently ... a saturated or unsaturated moiety having a linear, branched, or non-aromatic cyclic skeleton containing one to ten carbon atoms, zero to one nitrogen atoms, zero to four sulfur atoms and the carbon atoms are optionally substituted with...”

Thus, claim 75 permits R₂ to be a branched, unsaturated “skeleton” that contains up to 10 carbon atoms. Claim 75 is silent as to whether the “skeleton” can contain any oxygen atoms. However, given that the term “containing”, in reference to “skeleton”, is open-ended language, there is nothing to preclude the possibility that the “skeleton” can contain oxygen atoms. The term “skeleton” has no specific meaning with

regard to elemental composition. This may be contrasted with the term "alkylene", for example, the meaning of which is to exclude all atoms other than carbon and hydrogen. The term "skeleton" would imply simply that various atoms are linked together. Thus, if one began with the following "skeleton":



and replaced the methylene group with an oxygen atom, and the olefinic CH_2 group with an oxygen atom, the result would still be a "skeleton" falling within the scope of the claims; and that "skeleton" would be a t-Boc group.

Thus, the claim is anticipated.



Claims 22 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Falender (*Biocatalysis and Biotransformation* 13(2), 131-139, 1995).

Falender discloses the following compound on page 134 ("Ag" represents allylglycine):



The disclosed compound would be encompassed by claim 22 if the substituent variables could be as follows:

- R1 = allylglycine;
- R2 = hydrogen;
- R3 = hydrogen;

R4 = hydrogen;
R5 = phenyl;
R6 = hydrogen;
R7 = benzyl;
R8 = hydrogen;
Y = butene;
Z = -O-CH₂-CH₃

Claim 22 excludes allylglycine as a possibility for R1; however, R1 and R2 can both be hydrogen. This ground of rejection is justified because of the term "having" in the claim. This term permits additional substituents at the C- and/or N-terminus for the case of R1 and R2 both representing hydrogen.



Claims 22, 26, 61, 62, 75 are rejected under 35 U.S.C. §102(b) as being anticipated by Chang, L. L. (*Bioorganic & Medicinal Chemistry Letters* 2(10), 1207-12, 1992).

Chang discloses (page 1210) compound 25, which has the following structure ("Xaa" represents allylglycine):

Tyr-Val-Val-Asn-Asp-Xaa

The disclosed compound is encompassed by the instant claims when the substituent variables are as follows:

R1 = hydrogen;
R2 = hydrogen;

R3 = hydrogen;
R4 = hydrogen;
R5 = -CO-NH₂
R6 = hydrogen;
R7 = -CH₂-COOH
R8 = hydrogen;
Y = butene;
Z = -OH

When the substituent variables correspond as indicated above, the result is the following tripeptide: Asn-Asp-Xaa. However, the claim is drawn to a peptide "having" the indicated structure, rather than consisting of it. Accordingly, additional amino acids can be added to the N-terminus.



Claim 75 is rejected under 35 U.S.C. §102(e) as being anticipated by Webber (USP 6,214,799).

Webber teaches various compounds falling within the scope of claim 1. For example, at col 18, line 20+ a compound is taught. This corresponds to applicants' substituent variables as follows (R²⁰ is a variable created by the examiner):

Y = -CH(R²⁰)CH=CH- wherein R²⁰ is the side chain of glutamine;
Z = -O-C₂H₅;
R8 = hydrogen;
R7 = benzyl;
R6 = hydrogen;
R3 = hydrogen;
R5 = hydrogen;
R4 = alkyl;
R1 = hydrogen;

R2 = a benzyl group that is "substituted" with oxo (resulting in a benzoyl group)

Claim 75 permits "Y" to be a "skeleton" that "contains" 1-10 carbon atoms. Since the term "contains" (or "containing") is open-ended language, the claim would permit additional atoms to be present in the "skeleton".

Thus, the claim is anticipated.



Claims 75, 77, 78 are rejected under 35 U.S.C. §102(e) as being anticipated by Eisenbach-Schwartz (USP 6,126,939).

Eisenbach-Schwartz discloses (col 3, line 56) the following tripeptide: Glu-Arg-Ala.

R7 = the side chain of arginine
R5 = -CH₂-COOH;
R1 = hydrogen
R2 = hydrogen
Y = ethyl;
Z = OH

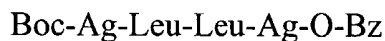
Unlike most of the other claims, claim 75 does not require "Y" to be an "unsaturated alkyl" group. Claim 75 permits variable R₉, together with the nitrogen atom to which it is bonded, to be a genetically encoded amino acid; that is, "Y" can be a "saturated moiety having a linear or branched...skeleton containing 1-10 carbon atoms",

and containing also any other atoms (such as nitrogen, hydrogen, sulfur and oxygen) which may be of interest. As such, claim 75 encompasses most known tripeptides (even apart from the issue of the term "having"). Eisenbach-Schwartz is one of many references which disclose tripeptides falling within the scope of claim 75.



Claims 22, 26, 61, 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Grubbs (USP 5,811,515).

Grubbs discloses the following compound at col 14, lines 10-22 ("Ag" represents allylglycine; "Bz" represents benzyl):



The disclosed compound would be encompassed by claim 22 if the substituent variables could be as follows:

R1 = allylglycine;
R2 = tBoc;
R3 = hydrogen;
R4 = hydrogen;
R5 = isopropyl;
R6 = hydrogen;
R7 = $\text{CH}_2\text{-CH}(\text{Me})_2$
R8 = hydrogen;
Y = butene;
Z = $-\text{O-CH}_2\text{-C}_6\text{H}_5$

Claim 22 does not permit R2 to be tBoc, or "Z" to be benzyloxy. However, the claim does permit R2 to be hydrogen, and "Z" to be -OH. At the same time, the claim is drawn to a peptide "having" the indicated structure. As such, additional functional groups can be added to the N-terminus and the C-terminus.

Thus, the claim is anticipated.



Claims 22, 26, 61, 75 are rejected under 35 U.S.C. §102(b) as being anticipated by Baldwin, Jack E. (*J. Chem. Soc., Chem. Comm.* (16), 1280-1, 1986).

Baldwin discloses compounds 8, 1(b), and 1(c). The abbreviation "AA" represents *alpha*-aminoadipoyl (p. 1280, col 1, bottom of page).

Any of the three cited compounds anticipates the claims.



The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the

obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claim 22 is rejected under 35 U.S.C. §103 as being unpatentable over Falender (*Biocatalysis and Biotransformation* 13(2), 131-139, 1995).

The teachings of Falender are indicated above. This ground of rejection is based on the possibility that at some point in the future, applicants will use the term "of", rather than "having" to describe the claimed genus. Should this event come to pass, this ground of rejection will go into effect. This ground of rejection is predicated on the assertion that the compound in which R₇ is phenylethyl would have been obvious, i.e., that the enzymologist of ordinary skill would have expected, *a priori*, substantially identical activity for the two homologs. [*In re Shetty* (195 USPQ 753) and *In re Hass & Susie* (60 USPQ 544)]. Accordingly, excluding the compound in which variable R₇ is benzyl will not be effective to overcome this ground of rejection.

Thus, the claim is rendered obvious.



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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1800